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(57) Abstract

Hydrogels of polymerized and crosslinked macromers comprising hydrophilic oligomers having biodegradable monomeric or oligomeric extensions, which biodegradable extensions are terminated on free ends with end cap monomers or oligomers capable of polymerization and cross linking are described. The hydrophilic core itself may be degradable, thus combining the core and extension functions. Macromers are polymerized using free radical initiators under the influence of long wavelength ultraviolet light, visible light excitation or thermal energy. Biodegradation occurs at the linkages within the extension oligomers and results in fragments which are non-toxic and easily removed from the body. Preferred applications for the hydrogels include prevention of adhesion formation after surgical procedures, controlled release of drugs and other bioactive species, temporary protection or separation of tissue surfaces, adhering of sealing tissues together, and preventing the attachment of cells to tissue surfaces.

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PHOTOPOLYMERIZABLE BIODEGRADABLE HYDROGELS AS TISSUE CONTACTING MATERIALS AND CONTROLLED-RELEASE CARRIERS

Field of the Invention

The present invention relates to photopolymerizable biodegradable hydrogels for use as tissue adhesives and in controlled drug delivery.

Background of the Invention

This is a continuation-in-part of U.S. Patent Application No. 07/843,485, filed February 28, 1992, entitled "Photopolymerizable Biodegradable Hydrogels as Tissue Contacting Materials and Controlled Release Carriers" by Jeffrey A. Hubbell, Chandrashekhar P. Pathak, and Amarpreet S. Sawhney.

Hydrogels as controlled-release carriers

Biodegradable hydrogels can be carriers for biologically active materials such as hormones, enzymes, antibiotics, antineoplastic agents, and cell suspensions. Temporary preservation of functional properties of a carried species, as well as controlled release of the species into local tissues or systemic circulation, are possible. Proper choice of hydrogel macromers can produce membranes with a range of permeability, pore sizes and degradation rates suitable for a variety of applications in surgery, medical diagnosis and treatment.

Adhesives and sealers

Fibrin gels have been used extensively in Europe as sealants and adhesives in surgery (Thompson *et al.*, 1988, "Fibrin Glue: A review of its preparation, efficacy, and adverse effects as a topical hemostat," *Drug Intell. and Clin. Pharm.*, 22:946; Gibble *et al.*, 1990, (1990), "Fibrin glue: the perfect operative sealant?" *Transfusion*, 30(8):741). However, they have not been used extensively in the United States

due to concerns relating to disease transmission from blood products. Synthetic polymers have been explored as adhesives (Lipatova, 1986, "Medical polymer adhesives," *Advances in Polymer Science* 79:65-93), but these materials have been associated with local inflammation, cytotoxicity, and poor biocompatibility.

Prevention of postoperative adhesions.

Formation of post-surgical adhesions involving organs of the peritoneal cavity and the peritoneal wall is a frequent and undesirable result of abdominal surgery. Surgical trauma to the tissue caused by handling and drying results in release of a serosanguinous (proteinaceous) exudate which tends to collect in the pelvic cavity (Holtz, G., 1984). If the exudate is not absorbed or lysed within this period it becomes ingrown with fibroblasts, and subsequent collagen deposition leads to adhesion formation.

Numerous approaches to elimination of adhesion formation have been attempted, with limited success in most cases. Approaches have included lavage of the peritoneal cavity, administration of pharmacological agents, and the application of barriers to mechanically separate tissues. For example, Boyers *et al.*, (1988) "Reduction of postoperative pelvic adhesions in the rabbit with Gore-Tex surgical membrane," *Fertil. Steril.*, 49:1066, examined Gore-Tex surgical membranes in the prevention of adhesions. For a review of adhesion prevention, see Holtz (1984) "Prevention and management of peritoneal adhesions," *Fertil. Steril.*, 41:497-507. However, none of these approaches has been cost effective and effective in *in vivo* studies.

Solutions of Poloxamer 407 have been used for the treatment of adhesions, with some success. Poloxamer is a copolymer of ethylene oxide and propylene oxide and is soluble in water; the solutions are liquids at

room temperature. Steinleitner *et al.* (1991) "Poloxamer 407 as an Intraperitoneal Barrier Material for the Prevention of Postsurgical Adhesion Formation and Reformation in Rodent Models for Reproductive Surgery," *Obstetrics and Gynecology*, 77(1):48 and Leach *et al.* (1990) "Reduction of postoperative adhesions in the rat uterine horn model with poloxamer 407, *Am. J. Obstet. Gynecol.*, 162(5):1317, examined Poloxamer solutions in peritoneal adhesion models and observed statistically significant reductions in adhesions; however, they were unable to eliminate adhesions, perhaps because of limited adhesion and retention on the injury site.

Oxidized regenerated cellulose has been used extensively to prevent adhesions and is an approved clinical product, trade-named Interceed TC7. This barrier material has been shown to be somewhat effective in rabbits (Linsky *et al.*, 1987 "Adhesion reduction in a rabbit uterine horn model using TC-7," *J. Reprod. Med.*, *32*:17; Diamond *et al.*, 1987 "Pathogenesis of adhesions formation/reformation: applications to reproductive surgery," *Microsurgery*, 8:103) and in humans (Interceed (TC7) *Adhesion Barrier Study Group*, 1989). It was shown to be more effective if pretreated with heparin, but was still unable to completely eliminate adhesions (Diamond *et al.*, 1991 "Synergistic effects of INTERCEED(TC7) and heparin in reducing adhesion formation in the rabbit uterine horn model," *Fertility and Sterility*, 55(2):389).

In summary, several lavage/drug/material approaches have been explored, but none of these approaches has been able to eliminate adhesions. An ideal material barrier would not evoke an adhesion response itself, stay in place without suturing (Holtz *et al.*, 1982 "Adhesion induction by suture of varying tissue reactivity and caliber," *Int. J. Fert.*, 27:134), degrade over a few weeks' time, effectively

reduce adhesions to very low extent, and be capable of delivering a drug to the local site of application for several days' time. None of the approaches developed and described to date meet these requirements.

Synthetic biodegradable polymers

The field of biodegradable polymers has developed rapidly since the synthesis and biodegradability of polylactic acid was first reported by Kulkarni *et al.*, 1966 "Polylactic acid for surgical implants," *Arch. Surg.*, 93:839. Several other polymers are known to biodegrade, including polyanhydrides and polyorthoesters, which take advantage of labile backbone linkages, as reported by Domb *et al.*, 1989 *Macromolecules*, 22:3200; Heller *et al.*, 1990 *Biodegradable Polymers as Drug Delivery Systems*, Chasin, M. and Langer, R., Eds., Dekker, New York, 121-161. Since it is desirable to have polymers that degrade into naturally occurring materials, polyaminoacids have been synthesized, as reported by Miyake *et al.*, 1974, for *in vivo* use. This was the basis for using polyesters (Holland *et al.*, 1986 *Controlled Release*, 4:155-180) of α-hydroxy acids (*viz.*, lactic acid, glycolic acid), which remain the most widely used biodegradable materials for applications ranging from closure devices (sutures and staples) to drug delivery systems (U.S. Patent No. 4,741,337 to Smith *et al.*; Spilizewski *et al.*, 1985 "The effect of hydrocortisone loaded poly(dl-lactide) films on the inflammatory response," *J. Control. Rel.* 2:197-203).

The time required for a polymer to degrade can be tailored by selecting appropriate monomers. Differences in crystallinity also alter degradation rates. Due to the relatively hydrophobic nature of these polymers, actual mass loss only begins when the oligomeric fragments are small enough to be water

soluble. Hence, initial polymer molecular weight influences the degradation rate.

Degradable polymers containing water-soluble polymer elements have been described. Sawhney et al., (1990) "Rapidly degraded terpolymers of dl-lactide, glycolide, and ϵ-caprolactone with increased hydrophilicity by copolymerization with polyethers," *J. Biomed. Mater. Res.* 24:1397-1411, copolymerized lactide, glycolide and ϵ-caprolactone with PEG to increase its hydrophilicity and degradation rate. U.S. Patent No. 4,716,203 to Casey et al. (1987) synthesized a PGA-PEG-PGA block copolymer, with PEG content ranging from 5-25% by mass. U.S. Patent No. 4,716,203 to Casey et al. (1987) also reports synthesis of PGA-PEG diblock copolymers, again with PEG ranging from 5-25%. U.S. Patent No. 4,526,938 to Churchill et al. (1985) described noncrosslinked materials with MW in excess of 5,000, based on similar compositions with PEG; although these materials are not water soluble. Cohn et al. (1988) *J. Biomed. Mater. Res.* 22:993-1009 described PLA-PEG copolymers that swell in water up to 60%; these polymers also are not soluble in water, and are not crosslinked. The features that are common to these materials is that they use both water-soluble polymers and degradable polymers, and that they are insoluble in water, collectively swelling up to about 60%.

Degradable materials of biological origin are well known, for example, crosslinked gelatin. Hyaluronic acid has been crosslinked and used as a degradable swelling polymer for biomedical applications (U.S. Patent No. 4,987,744 to della Valle et al., U.S. Patent 4,957,744 to Della Valle *et al.* (1991) "Surface modification of polymeric biomaterials for reduced thrombogenicity," *Polym. Mater. Sci. Eng.*, 62:731-735]).

Use of biodegradable materials for controlled drug release.

Most hydrophilic drugs are mechanically dispersed as suspensions within solutions of biodegradable polymers in organic solvents. Protein and enzyme molecular conformations are frequently different under these circumstances than they would be in aqueous media. An enzyme dispersed in such a hydrophobic matrix is usually present in an inactive conformation until it is released into the surrounding aqueous environment subsequent to polymer degradation. Additionally, some proteins may be irreversibly denatured by contact with organic solvents used in dispersing the protein within the polymer.

Polymer synthesis, degradation and local synthesis

Rapidly-degrading polymers currently suggested for short-term macromolecular drug release may raise local concentrations of potentially hazardous acidic degradation byproducts. Further, all biodegradable synthetic polymers reported thus far can only be processed in organic solvents and all biodegradable polymers are synthesized under conditions which are not amenable to polymerization *in vivo*. Thus, it has not been possible to make implantable materials as precisely conformed barriers, shaped articles, or membranes capable of delivering bioactive materials to the local tissue.

It is therefore an object of the present invention to provide hydrogels which are biocompatible, biodegradable, and can be rapidly formed by polymerization *in vivo*.

It is a further object of the present invention to provide a macromer solution which can be administered during surgery or outpatient procedures and polymerized as a tissue adhesive, tissue encapsulating medium, tissue support, or drug delivery medium.

It is a still further object of the present invention to provide a macromer solution which can be polymerized *in vivo* in a very short time frame and in very thin, or ultrathin, layers.

Summary of the Invention

Disclosed herein are biocompatible, biodegradable, polymerizable and at least substantially water soluble macromers, having a variety of uses *in vivo*. The macromers include at least one water soluble region, at least one region which is biodegradable, usually by hydrolysis, and at least two free radical-polymerizable regions. The regions can, in some embodiments, be both water soluble and biodegradable. The macromers are polymerized by exposure of the polymerizable regions to free radicals generated, for example, by photosensitive chemicals and dyes.

An important aspect of the macromers are that the polymerizable regions are separated by at least one degradable region to facilitate uniform degradation *in vivo*.. There are several variations of these polymers. For example, the polymerizable regions can be attached directly to degradable extensions or indirectly via water soluble nondegradable sections so long as the polymerizable regions are separated by a degradable section. For example, if the macromer contains a simple water soluble region coupled to a degradable region, one polymerizable region may be attached to the water soluble region and the other attached to the degradable extension or region. In another embodiment, the water soluble region forms the central core of the macromer and has at least two degradable regions attached to the core. At least two polymerizable regions are attached to the degradable regions so that, upon degradation, the polymerizable regions, particularly in the polymerized gel form, are

separated. Conversely, if the central core of the macromer is formed by a degradable region, at least two water soluble regions can be attached to the core and polymerizable regions attached to each water soluble region. The net result will be the same after gel formation and exposure to *in vivo* degradation conditions. In still another embodiment, the macromer has a water soluble backbone region and a degradable region affixed to the macromer backbone. At least two polymerizable regions are attached to the degradable regions, so that they are separated upon degradation, resulting in gel product dissolution. In a further embodiment, the macromer backbone is formed of a nondegradable backbone having water soluble regions as branches or grafts attached to the degradable backbone. Two or more polymerizable regions are attached to the water soluble branches or grafts. In another variation, the backbone may be star shaped, which may include a water soluble region, a biodegradable region or a water soluble region which is also biodegradable. In this general embodiment, the star region contains either water soluble or biodegradable branches or grafts with polymerizable regions attached thereto. Again, the polymerizable regions must be separated at some point by a degradable region.

Examples of these macromers are PEG-oligoglycolyl-acrylates. The choice of appropriate end caps permits rapid polymerization and gelation; acrylates were selected because they can be polymerized using several initiating systems, e.g., an eosin dye, by brief exposure to ultraviolet or visible light. The poly(ethyleneglycol) or PEG central structural unit (core) was selected on the basis of its high hydrophilicity and water solubility, accompanied by excellent biocompatibility. A short oligo or poly(α-hydroxy acid), such as polyglycolic

acid, was selected as a preferred chain extension because it rapidly degrades by hydrolysis of the ester linkage into glycolic acid, a harmless metabolite. Although highly crystalline polyglycolic acid is insoluble in water and most common organic solvents, the entire macromer is water-soluble and can be rapidly gelled into a biodegradable network while in contact with aqueous tissue fluids. Such networks can be used to entrap and homogeneously disperse water-soluble drugs and enzymes and to deliver them at a controlled rate. Further, they may be used to entrap particulate suspensions of water-insoluble drugs. Other preferred chain extensions are polylactic acid, polycaprolactone, polyorthoesters, and polyanhydrides. Polypeptides may also be used. Such "polymeric" blocks should be understood to include timeric, trimeric, and oligomeric blocks.

These materials are particularly useful for controlled drug delivery, especially of hydrophilic materials, since the water soluble regions of the polymer enable access of water to the materials entrapped within the polymer. Moreover, it is possible to polymerize the macromer containing the material to be entrapped without exposing the material to organic solvents. Release may occur by diffusion of the material from the polymer prior to degradation and/or by diffusion of the material from the polymer as it degrades, depending upon the characteristic pore sizes within the polymer, which is controlled by the molecular weight between crosslinks and the crosslink density. Deactivation of the entrapped material is reduced due to the immobilizing and protective effect of the gel and catastrophic burst effects associated with other controlled-release systems are avoided. When the entrapped material is an enzyme, the enzyme can be exposed to substrate while the enzyme is entrapped, provided the gel proportions are chosen to

allow the substrate to permeate the gel. Degradation of the polymer facilitates eventual controlled release of free macromolecules *in vivo* by gradual hydrolysis of the terminal ester linkages.

An advantage of these macromers are that they can be polymerized rapidly in an aqueous surrounding. Precisely conforming, semi-permeable, biodegradable films or membranes can thus be formed on tissue *in situ* to serve as biodegradable barriers, as carriers for living cells or other biologically active materials, and as surgical adhesives. In a particularly preferred embodiment, the macromers are applied to tissue having bound thereto an initiator, and polymerized to form ultrathin coatings. This is especially useful in forming coatings on the inside of tissue lumens such as blood vessels where there is a concern regarding restenosis, and in forming tissue barriers during surgery which thereby prevent adhesions from forming.

Examples demonstrate the use of these macromers and polymers for the prevention of postoperative surgical adhesions in rat cecum and rabbit uterine horn models. The polymer shows excellent biocompatibility, as seen by a minimal fibrous overgrowth on implanted samples. Hydrogels for the models were gelled in situ from water-soluble precursors by brief exposure to long wavelength ultraviolet (LWUV) light, resulting in formation of an interpenetrating network of the hydrogel with the protein and glycosaminoglycan components of the tissue. The degradable hydrogel was very effective, both by itself and in combination with tPA, in preventing adhesions.

Brief Description of the Drawings

Figure 1 shows schematically illustrated macromers of the present invention where _____ is a

water soluble core such as PEG; ~~~~~ is a hydrolyzably degradable extension such as a polyglycolide; ====== is a polymerizable end cap or side chain such as an acrylate; and ------ is a water-soluble and hydrolyzable portion such as a hyaluronate.

Figure 1A shows the degree of photopolymerization (dp) calculated and found by NMR.

Figure 2A shows Human foreskin fibroblasts cultured for six hours on glass coverslips coated with PEG 18.5K-glycolide diacrylate (18.5KG).

Figure 2B shows Human foreskin fibroblasts cultured for six hours on glass coverslips not coated with PEG.

Figure 3A shows the release of BSA from a PEG 1K (1000 molecular weight PEG) glycolide diacrylate with glycolide extensions (1 KG) hydrogel into PBS.

Figure 3B shows release of lysozyme from PEG 18.5K-DL-lactide tretraacrylate (18.5KL) into PBS.

Figure 4A shows release of active recombinant tPA from a PEG 1K lactide diacrylate (1KL) hydrogel.

Figure 4B shows release of active recombinant t-PA from PEG 4K glycolide diacrylate (4KG) hydrogel.

Figure 4C shows release of active recombinant tPA from a PEG 18.5K-glycolide diacrylate (18.5KG) hydrogel into PBS.

Figure 5A is a superior view of rabbit uterine horn used as a control. Distorted horn anatomy with 66% adhesions is evident. The horns are folded upon themselves.

Figure 5B is a superior view of rabbit uterine horn treated with a photopolymerized biodegradable hydrogel, PEG 18.5KL. Horn anatomy is normal, with no adhesion bands visible.

Figure 6A is an environmental scanning electron micrograph (ESEM) of an untreated blood vessel following trauma.

Figure 6B is an ESEM of a polymer coated blood vessel following trauma.

Description of the Preferred Embodiments

Disclosed herein are water soluble, biodegradable polymers formed from macromers containing both water soluble regions as well as biodegradable regions and at least two regions which are polymerizable by free radical initiation, preferably by photopolymerization using visible or long wavelength ultraviolet radiation.

The macromers.

In general terms, the macromers are polymers that are soluble in aqueous solutions, or nearly aqueous solutions, such as water with added dimethylsulfoxide. They have three components including a biodegradable region, preferably hydrolyzable under *in vivo* conditions, a water soluble region, and at least two polymerizable regions. Examples of these structures are shown in Figure 1.

Structure A in Figure 1 shows a macromer having a water soluble region (_____), a water soluble and degradable component (------) appended to one another. Each has a polymerizable end cap (======). Structure B shows a major water soluble component or core region (_____) extended at either end by a degradable or hydrolyzable component (~~~~~~) and terminated by, at either end, a polymerizable component (======). Structure C shows a central degradable or hydrolyzable component (~~~~~~) bound to a water soluble component (_____) capped at either end by a polymerizable component (======). Structure D shows a central water soluble component (_____) with numerous branches of hydrolyzable components (~~~~~~), each hydrolyzable component being capped with a polymerizable component (======). Structure E shows a central biodegradable, hydrolyzable component (~~~~~~) with three water

soluble branches (_____), each water soluble branch being capped by a polymerizable component (======). Structure F shows a long central water soluble and hydrolyzable component (------), each end being capped by a polymerizable component (======). Structure G shows a central water soluble and hydrolyzable component (------) capped at both ends by a hydrolyzable component (~~~~~~), each hydrolyzable component being capped by a polymerizable component (======). Structure H shows a central water soluble and degradable or hydrolyzable component (------) with end caps or branches of a polymerizable component (======). Structure I shows a central water soluble component (_____) in circular form with water soluble branches extended by a hydrolyzable component (~~~~~~) capped by a polymerizable component (======). Lastly, Structure J in Figure 1 shows a circular water soluble core component (_____) with degradable branches (~~~~~~), each being capped by a polymerizable component (~~~~~~).

The various structures shown in Figure 1 are exemplary only. Those skilled in the art will understand many other possible combinations which could be utilized for the purposes of the present invention.

Used herein is the term "at least substantially water soluble." This is indicative that the solubility should be at least about 1 g/100 ml of aqueous solution or in aqueous solution containing small amounts of organic solvent, such as dimethylsulfoxide. By the term "polymerizable" is meant that the regions have the capacity to form additional covalent bonds resulting in macromer interlinking, for example, carbon-carbon double bonds of acrylate-type molecules. Such polymerization is characteristically initiated by free-radical formation, for example, resulting from photon

absorption of certain dyes and chemical compounds to ultimately produce free-radicals.

In a preferred embodiment, a hydrogel begins with a biodegradable, polymerizable, macromer including a core, an extension on each end of the core, and an end cap on each extension. The core is a hydrophilic polymer or oligomer; each extension is a biodegradable polymer or oligomer; and each end cap is an oligomer, dimer or monomer capable of cross-linking the macromers. In a particularly preferred embodiment, the core includes hydrophilic poly(ethylene glycol) oligomers of molecular weight between about 400 and 30,000 Da; each extension includes biodegradable poly (α-hydroxy acid) oligomers of molecular weight between about 200 and 1200 Da; and each end cap includes an acrylate-type monomer or oligomer (i.e., containing carbon-carbon double bonds) of molecular weight between about 50 and 200 Da which are capable of cross-linking and polymerization between copolymers. More specifically, a preferred embodiment incorporates a core consisting of poly(ethylene glycol) oligomers of molecular weight between about 8,000 and 10,000 Da; extensions consisting of poly(lactic acid) oligomers of molecular weight about 250 Da; and end caps consisting acrylate moieties of about 100 Da molecular weight.

Those skilled in the art will recognize that oligomers of the core, extensions and end caps may have uniform compositions or may be combinations of relatively short chains or individual species which confer specifically desired properties on the final hydrogel while retaining the specified overall characteristics of each section of the macromer. The lengths of oligomers referred to herein may vary from two mers to many, the term being used to distinguish subsections or components of the macromer from the complete entity.

Water soluble regions.

In preferred embodiments, the core water soluble region can consist of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propyleneoxide) block copolymers, polysaccharides or carbohydrates such as hyaluronic acid, dextran, heparan sulfate, chondroitin sulfate, heparin, or alginate, proteins such as gelatin, collagen, albumin, ovalbumin, or polyamino acids.

Biodegradable regions.

The biodegradable region is preferably hydrolyzable under *in vivo* conditions. For example, hydrolyzable group may be polymers and oligomers of glycolide, lactide, ϵ-caprolactone, other hydroxy acids, and other biologically degradable polymers that yield materials that are non-toxic or present as normal metabolites in the body. Preferred poly(α-hydroxy acid)s are poly(glycolic acid), poly(DL-lactic acid) and poly(L-lactic acid). Other useful materials include poly(amino acids), poly(anhydrides), poly(orthoesters), poly(phosphazines) and poly(phosphoesters). Polylactones such as poly(ϵ-caprolactone), poly(ϵ-caprolactone), poly(δ-valerolactone) and poly(gamma-butyrolactone), for example, are also useful. The biodegradable regions may have a degree of polymerization ranging from one up to values that would yield a product that was not substantially water soluble. Thus, monomeric, dimeric, trimeric, oligomeric, and polymeric regions may be used.

Biodegradable regions can be constructed from polymers or monomers using linkages susceptible to biodegradation, such as ester, peptide, anhydride, orthoester, phosphazine and phosphoester bonds.

Polymerizable regions.

The polymerizable regions are preferably polymerizable by photoinitiation by free radical generation, most preferably in the visible or long wavelength ultraviolet radiation. The preferred polymerizable regions are acrylates, diacrylates, oligoacrylates, methacrylates, dimethacrylates, oligomethoacrylates, or other biologically acceptable photopolymerizable groups.

Other initiation chemistries may be used besides photoinitiation. These include, for example, water and amine initiation schemes with isocyanate or isothiocyanate containing macromers used as the polymerizable regions.

Photoinitiators and/or Catalysts.

Useful photoinitiators are those which can be used to initiate by free radical generation polymerization of the macromers without cytotoxicity and within a short time frame, minutes at most and most preferably seconds. Preferred dyes as initiators of choice for LWUV or visible light initiation are ethyl eosin, 2,2-dimethoxy-2-phenyl acetophenone, other acetophenone derivatives, and camphorquinone. In all cases, crosslinking and polymerization are initiated among macromers by a light-activated free-radical polymerization initiator such as 2,2-dimethoxy-2-phenylacetophenone or a combination of ethyl eosin (10^{-4} to 10^{-2} M) and triethanol amine (0.001 to 0.1 M), for example.

The choice of the photoinitiator is largely dependent on the photopolymerizable regions. For example, when the macromer includes at least one carbon-carbon double bond, light absorption by the dye causes the dye to assume a triplet state, the triplet state subsequently reacting with the amine to form a free radical which initiates polymerization. Preferred dyes for use with these materials include

eosin dye and initiators such as 2,2-dimethyl-2-phenylacetophenone, 2-methoxy-2-phenylacetophenone, and camphorquinone. Using such initiators, copolymers may be polymerized *in situ* by long wavelength ultraviolet light or by laser light of about 514 nm, for example.

Initiation of polymerization is accomplished by irradiation with light at a wavelength of between about 200-700 nm, most preferably in the long wavelength ultraviolet range or visible range, 320 nm or higher, most preferably about 514 nm or 365 nm.

There are several photooxidizable and photoreducible dyes that may be used to initiate polymerization. These include acridine dyes, for example, acriblarine; thiazine dyes, for example, thionine; xanthine dyes, for example, rose bengal; and phenazine dyes, for example, methylene blue. These are used with cocatalysts such as amines, for example, triethanolamine; sulphur compounds, for example, RSO_2R^1; heterocycles, for example, imidazole; enolates; organometallics; and other compounds, such as N-phenyl glycine. Other initiators include camphorquinones and acetophenone derivatives.

Thermal polymerization initiator systems may also be used. Such systems that are unstable at 37°C and would initiate free radical polymerization at physiological temperatures include, for example, potassium persulfate, with or without tetraamethyl ethylenediamine; benzoylperoxide, with or without triethanolamine; and ammonium persulfate with sodium bisulfite.

Applications for the Macromers.

Prevention of Surgical Adhesions.

A preferred application is a method of reducing formation of adhesions after a surgical procedure in a patient. The method includes coating damaged tissue surfaces in a patient with an aqueous solution of a

light-sensitive free-radical polymerization initiator and a macromer solution as described above. The coated tissue surfaces are exposed to light sufficient to polymerize the macromer. The light-sensitive free-radical polymerization initiator may be a single compound (e.g., 2,2-dimethoxy-2-phenyl acetophenone) or a combination of a dye and a cocatalyst (e.g., ethyl eosin and triethanol amine).

Controlled drug delivery.

A second preferred application concerns a method of locally applying a biologically active substance to tissue surfaces of a patient. The method includes the steps of mixing a biologically active substance with an aqueous solution including a light-sensitive free-radical polymerization initiator and a macromer as described above to form a coating mixture. Tissue surfaces are coated with the coating mixture and exposed to light sufficient to polymerize the macromer. The biologically active substance can be any of a variety of materials, including proteins, carbohydrates, nucleic acids, and inorganic and organic biologically active molecules. Specific examples include enzymes, antibiotics, antineoplastic agents, local anesthetics, hormones, antiangiogenic agents, antibodies, neurotransmitters, psychoactive drugs, drugs affecting reproductive organs, and oligonucleotides such as antisense oligonucleotides.

In a variation of the method for controlled drug delivery, the macromers are polymerized with the biologically active materials to form microspheres or nanoparticles containing the biologically active material. The macromer, photoinitiator, and agent to be encapsulated are mixed in an aqueous mixture. Particles of the mixture are formed using standard techniques, for example, by mixing in oil to form an emulsion, forming droplets in oil using a nozzle, or forming droplets in air using a nozzle. The

suspension or droplets are irradiated with a light suitable for photopolymerization of the macromer.

Tissue Adhesives.

Another use of the polymers is in a method for adhering tissue surfaces in a patient. The macromer is mixed with a photoinitiator or photoinitiator/cocatalyst mixture to form an aqueous mixture and the mixture is applied to a tissue surface to which tissue adhesion is desired. The tissue surface is contacted with the tissue with which adhesion is desired, forming a tissue junction. The tissue junction is then irradiated until the macromers are polymerized.

Tissue Coatings.

In a particularly preferred application of these macromers, an ultrathin coating is applied to the surface of a tissue, most preferably the lumen of a tissue such as a blood vessel. One use of such a coating is in the treatment or prevention of restenosis, abrupt reclosure, or vasospasm after vascular intervention. The photoinitiator is applied to the surface of the tissue, allowed to react, adsorb or bond to tissue, the unbound photoinitiator is removed by dilution or rinsing, and the macromer solution is applied and polymerized. As demonstrated below, this method is capable of creating uniform polymeric coating of between one and 500 microns in thickness, most preferably about twenty microns, which does not evoke thrombosis or localized inflammation.

Tissue Supports.

The macromers can also be used to create tissue supports by forming shaped articles within the body to serve a mechanical function. Such supports include, for example, sealants for bleeding organs, sealants for bone defects and space-fillers for vascular aneurisms. Further, such supports include strictures

to hold organs, vessels or tubes in a particular position for a controlled period of time.

The following examples are presented to describe preferred embodiments and utilities of the present invention and are not meant to limit the invention unless otherwise stated in the claims appended hereto. Taken together, the examples illustrate representative demonstrations of the best mode of implementing the invention as currently understood.

Table 1 shows the code names of the various macromers synthesized in or for use in the examples, along with their composition in terms of the molecular weight of the central PEG segment and the degree of polymerization of the degradable comonomer.

Table 1: Macromer Molecular Weight and Composition.

PEG molecular weight	Comonomer	D.P. of conomoner per OH group	Polymer Code
20,000	glycolide	15	20KG
18,500	glycolide	2.5	18.5K
10,000	glycolide	7	10KG
6,000	glycolide	5	6KG
4,000	glycolide	5	4KG
1,000	glycolide	2	1KG
20,000	DL-lactide	10	20KL
18,500	DL-lactide	10	18.5KL
10,000	DL-lactide	5	10KL
6,000	DL-lactide	5	6KL
1,000	DL-lactide	2	1KL
600	DL-lactide	2	0.6KL
600	DL-lactide + caprolactone(CL)	lactide 2; CL 1	0.6KLCL
18,500	caprolactone	2.5	18.5KCL
18,500	-	-	18.5KCO

Example 1: Synthesis of Photopolymerized Biodegradable Hydrogels.

PEG-based hydrogels

PEG-based biodegradable hydrogels are formed by the rapid laser or UV photopolymerization of water soluble macromers. Macromers, in turn, are synthesized by adding glycolic acid oligomers to the end groups of PEG and then capping with acrylic end groups. The PEG portions of the macromers confer water solubility properties, and subsequent polymerization results in cell-nonadhesive hydrogels. Glycolic acid oligomers serve as the hydrolyzable fraction of the polymer network, while acrylic end groups facilitate rapid polymerization and gelation of the macromers.

In preparation for synthesis, glycolide (DuPont) or DL-lactide (Aldrich) was freshly recrystallized from ethyl acetate. PEG oligomers of various molecular weight (Fluka or Polysciences) were dried under vacuum at 110°C prior to use. Acryloyl chloride (Aldrich) was used as received. All other chemicals were of reagent grade and used without further purification.

Macromer synthesis

A 250 ml round bottom flask was flame dried under repeated cycles of vacuum and dry argon. 20 gm of PEG (molecular weight 10,000), 150 ml of xylene and 10 μgm of stannous octoate were charged into the flask. The flask was heated to 60°C under argon to dissolve the PEG and cooled to room temperature. 1.16 gm of glycolide was added to the flask and the reaction mixture was refluxed for 16 hr. The copolymer was separated on cooling and was recovered by filtration. This copolymer was separated on cooling and recovered by filtration. This copolymer (10K PEG-glycolide) was used directly for subsequent reactions. Other polymers were similarly synthesized

using DL-lactide or ε-caprolactone in place of glycolide and using PEG of different molecular weights.

Synthesis of photosensitive oligomers (macromers):

19 gm of 10K PEG-glycolide copolymer was dissolved in 150 ml methylene chloride and refluxed with 1 ml acryloyl chloride and 1.2 ml of triethylamine for 12 hr under an argon atmosphere. The solid triethylamine hydrochloride was separated by filtration and the polymer was precipitated by adding the filtrate to a large excess of hexane. The polymer (capped by an acrylate at both ends) was further purified by repeated dissolution and precipitation in methylene chloride and hexane respectively.

Table 2 lists certain macromers synthesized. The degree of polymerization of the glycolide chain extender was kept low so that all polymers have approximately 10 ester groups per chain, or about 5 per chain end. When these polymers are photopolymerized, a crosslinked three-dimensional network is obtained. However, each chain segment in the resulting network needs just one ester bond cleaved at either end to "degrade." These ester cleavages enable the chain to dissolve in the surrounding physiological fluid and thereby be removed from the implant site. The resulting hydrolysis products, PEG and glycolic acid, are water soluble and have very low toxicity.

TABLE 2: Macromers Synthesized

Polymer Code	Mol. Wt. of Central PEG Chain (daltons)	%Glycolide in Extremeties	% ε-Caprolactone in Extremities	Calculated Mol. Wt. of Extremities (daltons)	Appearance
0.4K	400	100	-	580	Viscous liquid
1KG	1000	100	-	300	Viscous liquid
4KG	4000	100	-	232	White solid
10KG	10000	100	-	580	White solid
18.5KG	18500	100	-	1160	Yellow solid
col8.5KGCL	18500	50	-	580	White solid

Due to the presence of only a few units of glycolic acid per oligomeric chain, the solubility properties of the photocrosslinkable prepolymers are principally determined by the central PEG chain. Solubility of the macromers in water and methylene chloride, both of which are solvents for PEG, is not adversely affected as long as the central PEG segment has a molecular weight of 1,000 daltons or more. Solubility data for the prepolymers synthesized is given in Table 3.

Table 3: SOLUBILITY DATA

Solvent	1KG	4KG	10KG	18.5KG	TMP*
DMSO	–	■	–	■	■
Acetone	–	■	■	■	–
Methanol	–	■	–	■	–
Water	–	–	–	–	■
Hexane	■	■	■	■	■
Methylene Chloride	–	–	–	–	–
Cold Xylene	■	■	■	■	–
Hot Xylene	–	–	–	–	–
Benzene	■	■	■	■	–

– Soluble

■ Not Soluble

* Trimethylolpropane glycolide triacrylate

PEG chains with different degrees of polymerization of DL-lactide were synthesized to determine the degree of substitution for which water solubility of the macromers can be retained. The results are shown in Table 4. Beyond about 20% substitution of the hydrophilic PEG chain with hydrophobic DL-lactoyl or acrylate terminals leads to the macromers becoming insoluble in water, though they

are still soluble in organic solvents such as methylene chloride.

Table 4: Solubility of Macromers

D.P.* of Ethylene Oxide	D.P.* of lactide or glycolide	% extension of PEG chain	Solubility in water
420	4	0.1	soluble
420	10	2.4	soluble
420	20	4.8	soluble
420	40	9.5	soluble
420	80	19	insoluble
23	2	8.7	soluble
23	4	17.4	soluble
23	10	43.5	insoluble
23	40	174	insoluble
5	4	80	insoluble
10	4	40	soluble

* degree of polymerization

Photopolymerization

The macromers can be gelled by photopolymerization using free radical initiators, with the presence of two acrylic double bonds per chain leading to rapid gelation. A 23% w/w solution of various degradable polymers in HEPES buffered saline containing 3 μl of initiator solution (300 mg/ml of 2,2-dimethoxy-2-phenyl-acetophenone in n-vinyl pyrrolidone) was used. 100 μl of the solution was placed on a glass coverslip and irradiated with a low intensity long wavelength UV (LWUV) lamp (Blak-Ray, model 3-100A with flood). The times required for gelation to occur were noted and are given below. These times are typically in the range of 10 seconds. This is very significant because these reactions are carried out in air (UV initiated photopolymerizations are slow in air as compared to an inert atmosphere)

and using a portable, low powered long wave UV (LWUV) emitting source. Oxygen, which often inhibits free radical reactions by forming species which inhibit propagation, did not seem to slow down the polymerization. Such fast polymerizations are particularly useful in applications requiring *in situ* gelations. This rapid gelation is believed to be due to the formation of micelle-like structures between the relatively hydrophobic polymerizable groups on the macromer, thereby increasing the local concentration of the polymerizable species in aqueous solution and increasing polymerization rates.

Visible laser light is also useful for polymerization. Low intensity and short exposure times make visible laser light virtually harmless to living cells since the radiation is not strongly absorbed in the absence of the proper chromophore. Laser light can also be transported using fiber optics and can be focused to a very small area. Such light can be used for rapid polymerization in highly localized regions; gelation times for selected prepolymers are given in Table 5. In each case, 0.2 ml of a 23% w/v photosensitive oligomer solution is mixed with ethyl eosin (10^{-4} M) and triethanol amine (0.01 to 0.1 M) and the solution is irradiated with an argon ion laser (American argon ion laser model 905 emitting at 514 nm) at a power of 0.2-0.5 W/cm^2. The beam is expanded to a diameter of 3 mm and the sample is slowly scanned until gelation occurs.